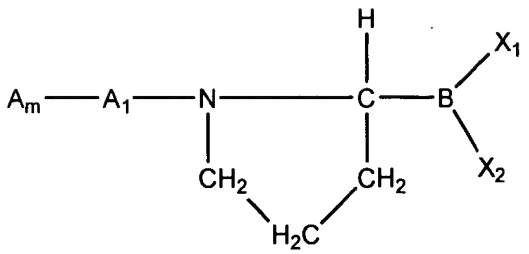


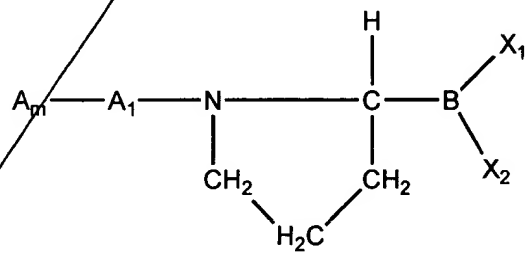
wherein m is an integer between 0 and 10, inclusive; A and A_1 are L- or D-amino acid residues; and each X_1 and X_2 is independently a hydroxyl group or a group capable of being hydrolyzed to a hydroxyl group in aqueous solution at physiological pH,

at least one other anti-cancer compound, and

a pharmaceutically acceptable carrier.

37. (Amended) A pharmaceutical preparation comprising:

an agent of Formula II



wherein m is an integer between 0 and 10, inclusive; A and A_1 are L- or D-amino acid residues; and each X_1 and X_2 is independently a hydroxyl group or a group capable of being hydrolyzed to a hydroxyl group in aqueous solution at physiological pH,

at least one other anti-angiogenic compound, and

a pharmaceutically acceptable carrier.

Remarks

The specification has been amended to state, where known, the status of cited patent applications.

Claims 1, 19, 36 and 37 have been amended to recite Formula II compounds. Support for this amendment can be found in the specification on page 2, lines 26-30 and page 3, lines 1-7. Claims 1 and 19 have been further amended to recite administration of a compound selected from the group consisting

of an anti-cancer compound and an anti-angiogenic compound. Support for this amendment can be found in the claims as originally filed and in the specification on page 6, lines 12-16.

Applicants reserve the right to pursue the subject matter of the originally filed claims in a continuing application.

No new matter has been added.

Rejection under 35 U.S.C. 112, second paragraph

Claims 1-8, 11-17, 19, 31, 36 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The claims have been rejected because they do not recite what constitutes "Formula I." Applicants have amended claims 1, 19, 36 and 37 to recite Formula II and to include the structure of Formula II compounds as described in the specification.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. 102(b)

In view of Powers et al. (USP 5,543,396)

Claims 1, 2, 15 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Powers et al. (USP 5,543,396). According to the Examiner, Powers et al. teach the use of DPP-IV inhibitors that satisfy Formula I to control tumor invasion.

Powers et al. teach peptidyl derivatives of aromatic diesters of α-aminoalkylphosphonic acids that inhibit some serine proteases. The reference states that these compounds can be used to control tumor invasion. The reference also states that these compounds can be used to inhibit DPP-IV and, in doing so, would be useful in organ transplant rejection, treatment of AIDS and other immune system disorders. The reference does not teach that inhibition of DPP-IV would be useful in tumor invasion. The reference also does not identify FAP as a target of the disclosed inhibitors.

Applicants have amended claims 1 and 19 to recite compounds of Formula II, a category of compounds not taught by Powers et al. The pending claims are not anticipated by Powers et al.

In view of Kinder et al. (USP 4,963,655)

Claims 1, 2, 5, 7, 15 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Kinder et al. (USP 4,963,655). According to the Examiner, Kinder et al. teach protease inhibitors with structural and functional similarity to the compounds of Formula I, and thus are "deemed inherently to comprise a targeting group which binds to the reactive site of FAPα or other post-proline cleaving enzyme and to

comprise a reactive group capable of reacting with a functional group in FAPα or other post-proline cleaving enzyme." The Examiner states that the burden rests with the Applicants to show that "compounds of Formula I are unobviously different" from the inhibitors taught by Kinder et al.

Kinder et al. teach that select compounds containing boroVal, boroAla and boroPhenylalanine can be used to inhibit protease activity, and growth and colony formation of cancer cells in vitro. The reference teaches that proteases have been reportedly associated with cancer-related processes, but it does not specifically identify these proteases, nor does it identify which proteases are targeted by the disclosed inhibitors. The reference teaches that "other protease inhibitors have been evaluated .. as antitumour agents, always with disappointing results."

Applicants rebut the Examiner's assertion that the burden rests with Applicants to disprove that the Kinder et al. compounds are Formula I compounds. The Examiner puts forth no evidence in support of his inherency argument.

Regardless, Applicants have amended claims 1 and 19 to recite compounds of Formula II, a category of compounds not taught by Powers et al. The pending claims are not anticipated by Kinder et al.

In view of WO95/15309

Claims 1, 2, 4-7, 15 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by WO95/15309. According to the Examiner, WO95/15309 teaches subjects, agents and method steps that are the same as the claims as previously pending.

WO95/15309 teaches inhibitors of DP-IV mediated processes. The reference reports that lung endothelial DP-IV is an adhesion molecule for lung metastatic rat breast and prostate carcinoma cells, and that some DP-IV inhibitors (e.g., Group II inhibitors) are useful in preventing lung metastasis of breast and prostate tumors. Other DP-IV inhibitors (e.g., Group I) are useful as immunosuppressants and as anti-HIV agents. The reference does not teach that these compounds would be useful as anti-angiogenic or anti-proliferative compounds.

Applicants have amended claims 1 and 19 to recite compounds of Formula II, a category of compounds not taught by WO95/15309. The pending claims are not anticipated by WO95/15309.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. 103(a)

In view of Powers et al. (USP 5,543,396)

Claims 11, 16 and 17 are rejected under 35 U.S.C. 103(a) as being obvious over Powers et al. (USP 5,543,396). According to the Examiner, although "Powers et al. do not set forth any limitations on the type of subjects who can be treated to control tumor invasion ... it would have been obvious ... to control tumor invasion according to the methods of Powers et al. in any subject ... because it is desirable to control tumor invasion in any patient in which tumors are found, and because the hemopoietic activity or HIV status of each patient would not have been expected adversely to affect the patient's ability to be treated in the method of Powers et al."

The Powers et al. reference has been discussed above. Powers et al. do not teach compounds that satisfy Formula II as currently recited in claim 1 (from which claims 11, 16 and 17 depend). Accordingly, these claims are not rendered obvious from the teaching of Powers et al.

In view of Powers et al. (USP 5,543,396) and O'Reilly et al. (USP 5,854,205) or Brooks et al. (USP 5,753,230)

Claims 12-14, 31, 36 and 37 are rejected under 35 U.S.C. 103(a) as being obvious over Powers et al. (USP 5,543,396), in view of O'Reilly et al. (USP 5,854,205) or Brooks et al. (USP 5,753,230). According to the Examiner, although Powers et al. do not disclose combinations of their disclosed inhibitors with anti-cancer or anti-angiogenic compounds, or surgical methods, O'Reilly et al. and Brooks et al. "disclose that it is known to combine surgical, chemotherapeutical, and anti-angiogenic treatments in treating tumors." The Examiner concludes that it is would have been obvious to combine the tumor treatment of Powers et al. with other tumor treatment methods because O'Reilly and Brooks et al. "show it is routine in the cancer therapy arts to combine treatments in order to optimize treatment of the cancer."

The Powers et al. reference has been discussed above. The O'Reilly et al. and Brooks et al. references respectively deal with endostatin and vitronectin antagonists as anti-angiogenic compounds. Neither of these compound classes satisfies Formula I or II. O'Reilly teaches that endostatin can be used in combination with surgery, radiation or chemotherapy. Brooks teaches that vitronectin antagonists can be used in combination with other therapies including chemotherapy or surgery (as prophylaxis). The references do not teach the combination of anti-angiogenic compounds generally with surgery or chemotherapy. Rather the teachings of O'Reilly et al. and Brooks et al. are specific for endostatin and vitronectin antagonists.

Applicants have amended claims 1, 19, 36 and 37 to recite a compound of Formula II which is not taught by Powers et al. O'Reilly et al. and Brooks et al. also do not teach such a compound. Accordingly, claims 12-14, 31, 36 and 37 are not rendered obvious by the teaching of Powers et al. combined with either O'Reilly et al. or Brooks et al.

In view of Kinder et al. (USP 4,963,655)

Claims 11, 16 and 17 are rejected under 35 U.S.C. 103(a) as being obvious over Kinder et al. (USP 4,963,655). According to the Examiner, although "Kinder et al. do not set forth any limitations on the type of subjects who can be treated to control tumor invasion ... it would have been obvious ... to treat tumors according to the methods of Kinder et al. in any subject ... because it is desirable to treat tumors in any patient in which tumors are found, and because the hemopoietic activity or HIV status of such a patient would not have been expected adversely to affect the patient's ability to be treated in the method of Kinder et al."

The Kinder et al. reference has been discussed above. Kinder et al. do not teach compounds that satisfy Formula II as currently recited in claim 1 (from which claims 11, 16 and 17 depend). Accordingly, these claims are not rendered obvious from the teaching of Kinder et al.

In view of Kinder et al. (USP 4,963,655) and O'Reilly et al. (USP 5,854,205) or Brooks et al. (USP 5,753,230)

Claims 12-14, 31, 36 and 37 are rejected under 35 U.S.C. 103(a) as being obvious over Kinder et al. (USP 4,963,655), in view of O'Reilly et al. (USP 5,854,205) or Brooks et al. (USP 5,753,230). According to the Examiner, although Kinder et al. do not disclose combinations of their disclosed inhibitors with anti-cancer or anti-angiogenic compounds, or surgical methods, O'Reilly et al. and Brooks et al. "disclose that it is known to combine surgical, chemotherapeutical, and anti-angiogenic treatments in treating tumors." The Examiner concludes that it is would have been obvious to combine the tumor treatment of Kinder et al. with other tumor treatment methods because O'Reilly and Brooks et al. "show it is routine in the cancer therapy arts to combine treatments in order to optimize treatment of the cancer."

The Kinder et al., O'Reilly et al. and Brooks et al. references have been discussed above.

Applicants have amended claims 1, 19, 36 and 37 to recite a compound of Formula II which is not taught by Kinder et al. O'Reilly et al. and Brooks et al. also do not teach such a compound. Accordingly, claims 12-14, 31, 36 and 37 are not rendered obvious by the teaching of Kinder et al. combined with either O'Reilly et al. or Brooks et al.

In view of WO95/15309

Claims 11, 16 and 17 are rejected under 35 U.S.C. 103(a) as being obvious over WO95/15309. According to the Examiner, although WO95/15309 "does not set forth any limitations on the type of subjects who can be treated for breast and prostate tumors and to prevent metastases ... it would have been obvious ... to treat breast and prostate tumors and to prevent metastases according to the method of WO95/15309 in any subject ... because it is desirable to treat breast and prostate tumors and to prevent

metastases in any patient in which tumors are found, and because the hemopoietic activity or HIV status of such a patient would not have been expected adversely to affect the patient's ability to be treated in the method of WO95/15309."

The WO95/15309 reference has been discussed above. WO95/15309 does not teach compounds that satisfy Formula II as currently recited in claim 1 (from which claims 11, 16 and 17 depend). Accordingly, these claims are not rendered obvious from the teaching of WO95/15309.

In view of WO95/15309 and O'Reilly et al. (USP 5,854,205) or Brooks et al. (USP 5,753,230)

Claims 12-14, 31, 36 and 37 are rejected under 35 U.S.C. 103(a) as being obvious over WO95/15309, in view of O'Reilly et al. (USP 5,854,205) or Brooks et al. (USP 5,753,230). According to the Examiner, although WO95/15309 does not teach combinations of the disclosed inhibitors with anti-cancer or anti-angiogenic compounds, or surgical methods, O'Reilly et al. and Brooks et al. "disclose that it is known to combine surgical, chemotherapeutical, and anti-angiogenic treatments in treating tumors." The Examiner concludes that it is would have been obvious to combine the tumor treatment of WO95/15309 with other tumor treatment methods because O'Reilly and Brooks et al. "show it is routine in the cancer therapy arts to combine treatments in order to optimize treatment of the cancer."

The WO95/15309, O'Reilly et al. and Brooks et al. references have been discussed above.

Applicants have amended claims 1, 19, 36 and 37 to recite a compound of Formula II which is not taught by WO95/15309. O'Reilly et al. and Brooks et al. also do not teach such a compound. Accordingly, claims 12-14, 31, 36 and 37 are not rendered obvious by the teaching of WO95/15309 combined with either O'Reilly et al. or Brooks et al.

In view of Zimmerman et al. (USP 5,767,242) and Bachovchin (USP 5,965,532)

Claims 1-8, 15 and 18 are rejected under 35 U.S.C. 103(a) as being obvious over Zimmerman et al. (USP 5,767,242) in view of Bachovchin (USP 5,965,532). According to the Examiner, Zimmerman et al. do not teach compounds of Formula I or Val-boroPro as FAPα inhibitors, but "it would have been obvious to use an inhibitor of such a structure ... to inhibit FAPα ... because the most common structure for an enzyme inhibitor is a ligand bound to a reactive group." The Examiner also states that "because of the analogous structures of FAPα and DPP-IV, and because inhibitors of one enzyme are commonly used to inhibit other enzymes .. of the same class, it would have been obvious to .. use Val-boroPro, which Bachovchin teaches is a known inhibitor with the highest affinity for DPP-IV..., to inhibit FAPα and thereby treat cancer according to the method of Zimmerman et al."

Zimmerman et al. report the cloning and isolation of FAPα coding nucleic acids. The reference teaches that human DPP-IV has 51% nucleic acid identity and 52% amino acid identity to FAPα. The

reference further teaches that FAPα may be targeted in order to treat cancerous and precancerous conditions, and that FAPα inhibitors that are substrate derivatives of FAPα (such as modified collagen molecules) could be used therapeutically. The reference does not teach that inhibitors of other proteases (and in particular DPP-IV) could function as FAPα inhibitors.

Bachovchin teaches that transition state analog based compounds such as ProboroPro, AlaboroPro and ValboroPro are inhibitors of DP-IV. The reference does not teach that these compounds are effective inhibitors of FAPα.

The Examiner has failed to make a prima facie case of obvious because there is no motivation to combine the references for several reasons. First, the Examiner provides no evidence in support of his assertion that inhibitors of one enzyme are commonly used to inhibit other enzymes of the same class. Rather, it is commonly accepted that enzymes are generally highly substrate specific, and thus would be expected to be highly inhibitor specific, particularly if the inhibitor is substrate derived. Second, in view of the teaching of Zimmerman et al. that FAPα and DP-IV share only 51% nucleic acid and 52% amino acid identity, there is no reasonable expectation that DP-IV inhibitors would function as FAPα inhibitors. Third, although Zimmerman et al. suggest the therapeutic utility of FAPα inhibitors that are substrate derived, the reference teaches modified collagen compounds, and not boroPro containing compounds as taught by Bachovchin, as putative inhibitors.

In combining the references as the Examiner has, he is relying on an "obvious to try" rationale. That is, while the DP-IV inhibitors taught by Bachovchin might be tested for their ability to inhibit FAPα (just as a variety of other protease inhibitors could similarly be tested), there is no reasonable expectation that such compounds would inhibit FAPα. The Examiner is also engaging in impermissible hindsight when combining the Zimmerman et al. and Bachovchin references because there is nothing in either reference to suggest that the compounds of Bachovchin would inhibit the enzyme of Zimmerman et al. Accordingly, the Examiner has not set forth a prima facie case of obviousness because there exists no motivation to combine the references and so arrive at the claimed invention.

In view of Zimmerman et al. (USP 5,767,242) and Bachovchin (USP 5,965,532)

Claims 11, 16 and 17 are rejected under 35 U.S.C. 103(a) as being obvious over Zimmerman et al. (USP 5,767,242) in view of Bachovchin (USP 5,965,532). According to the Examiner, although "Zimmerman et al. do not set forth any limitations on the type of subjects who can be treated for cancer ... it would have been obvious ... to treat breast and prostate tumors and to prevent metastases according to the method of Zimmerman et al. as modified above by Bachovchin in any subject ... because it is desirable to treat tumors in any patient in which tumors are found, and because the hemopoietic activity or

HIV status of such a patient would not have been expected adversely to affect the patient's ability to be treated in the method of Zimmerman et al. in view of Bachovchin."

The Zimmerman et al. and Bachovchin references have been discussed above. As stated above, the Examiner has not made a prima facie case of obviousness in view of Zimmerman et al. and Bachovchin for claim 1 (from which claims 11, 16 and 17 depend). Accordingly, a prima facie case of obvious has also not been made with respect to these latter claims.

In view of Zimmerman et al. (USP 5,767,242) and Bachovchin (USP 5,965,532) and O'Reilly et al. (USP 5,854,205) or Brooks et al. (USP 5,753,230)

Claims 12-14, 19, 31, 36 and 37 are rejected under 35 U.S.C. 103(a) as being obvious over Zimmerman et al. (USP 5,767,242) and Bachovchin (USP 5,965,532), in view of O'Reilly et al. (USP 5,854,205) or Brooks et al. (USP 5,753,230). According to the Examiner, although Zimmerman et al. do not disclose combinations of "their disclosed inhibitors" with anti-cancer or anti-angiogenic compounds, or surgical methods, O'Reilly et al. and Brooks et al. "disclose that it is known to combine surgical, chemotherapeutical, and anti-angiogenic treatments in treating tumors." The Examiner concludes that it is would have been obvious to combine the tumor treatment of Zimmerman et al. as modified above by Bachovchin with other tumor treatment methods because O'Reilly and Brooks et al. "show it is routine in the cancer therapy arts to combine treatments in order to optimize treatment of the cancer."

The Zimmerman et al., Bachovchin, O'Reilly et al. and Brooks et al. references have been discussed above. As stated above, the Examiner has not made a prima facie case of obviousness in view of Zimmerman et al. and Bachovchin, and accordingly claims 12-14, 19, 31, 36 and 37 are not rendered obvious in view of these references.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 103(a).

Summary

Applicants believe that each of the pending claims is in condition for allowance. Applicants respectfully request that the Examiner telephone Applicants' agent in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions and believes that a telephone conference with Applicants' agent would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (extension 266).

Respectfully Submitted,

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(617)720-3500

Docket No.: I0248/7012 (ERG/MAT)
Date: December 31, 2001
x12/29/01

APPENDIX A

MARKED-UP SPECIFICATION

Please amend the specification as follows:

Please re-write the paragraph starting on page 13, line 14, as follows:

As mentioned earlier, the agents, including their individual targeting and reactive groups, may be synthesized using recombinant or chemical library synthesis approaches. Libraries of interest in the invention include peptide libraries, synthetic organic combinatorial libraries, and the like. The artisan or ordinary skill is familiar with the methodology for library and combinatorial chemistry synthesis as well as the screening of such compounds for agents which are useful in the methods of the invention. The use of library technology, such as phage display, and combinatorial chemistry, such as compound array methods, in the synthesis and screening of protease inhibitors has been previously described in U.S. Patent Application entitled "Multivalent Compounds for Crosslinking Receptors and Uses Thereof " filed on April 12, 1999 and assigned U.S.S.N. 09/290,376 (pending), the contents of which are incorporated in their entirety by reference. Examples of parallel synthesis mixtures and parallel synthesis methods are provided in U.S.S.N. 08/177,497, filed January 5, 1994 and its corresponding PCT published patent application W095/18972, published July 13, 1995 and U.S. Patent No. 5,712,171 granted January 27, 1998 and its corresponding PCT published patent application W096/22529, which are hereby incorporated by reference.

Please re-write the paragraph starting on page 18, line 9, as follows:

The method, in one embodiment, intends to treat subjects free of symptoms calling for hemopoietic stimulation, by administering compounds of Formula I in an amount effective to inhibit proliferation. The ability to treat subjects having symptoms calling for hemopoietic stimulation with the some of compounds (e.g., ValboroPro) described herein has been previously disclosed in U. S. Patent Application entitled "Hematopoietic Stimulation", Serial No. 09/304,199, filed May 3, 1999, now issued as U.S. Patent No. 6,300,314, issued October 9, 2001, the contents of which are incorporated herein in their entirety by reference. Thus, the instant invention intends, in certain embodiments, to treat subjects at a time when they are free of symptoms requiring hemopoietic stimulating treatment or to treat subjects who have such symptoms with amounts or dosages or administration schedules that differ from those used to protect or restore normal or protective levels of hemopoietic cells. A subject who has previously experienced a need for hemopoietic stimulation but has since recovered its hemopoietic cells to normal or at least protective levels may still be treated by the methods described herein.

Please re-write the paragraph starting on page 39, line 9, as follows:

Agents useful in the invention can be identified using a screening assay method for determining whether a putative agent is able to inhibit the activity of FAP-α, thereby inhibiting cell proliferation. The initial screening assay can be conducted in an in vitro system with a readout of FAP-α inhibition. In such screening assays, cells expressing FAP-α but not CD26 can be used as a source of FAP-α. Alternatively, recombinant or purified FAP-α can also be used in either a soluble or bound form. The choice of whether to use FAP-α in either a soluble or bound form may depend upon the source of the compounds to be screened. For example, if the compounds to be screened are present in phage libraries, it may be desirable to use soluble FAP-α. If, on the other hand, the compounds are synthesized by combinatorial chemistry techniques, then bound FAP-α may be more suitable. It is possible to immobilize FAP-α in 96 well plates through either direct binding to the surface, or more preferably through the indirect binding via an anti-FAP-α antibody or antibody fragment such as that derived from F19, a FAP-α specific antibody. Binding is achieved through incubation at room temperature for 2 hours, followed by washing with a phosphate buffered saline solution containing a suitable non-specific blocking agent such as albumin or serum. After significant washing, the substrate alanylprolyl-7-amido-4-trifluoromethyl-coumarin (Ala-Pro--NH-F3-Mec, available from Bachem) is added to the plates and incubated for 1 hour at 37°C in 100 mM Tris/HCl, pH7.8, 100 mM NaCl. At the end of the incubation, a fluorometric measurement is made for each well using an excitation wavelength of 390 nm and an emission wavelength of 538 nm. The substrate described above can also be used in soluble FAP-α enzyme inhibition assays are described in U.S. Patent Application entitled "Multivalent Compounds for Crosslinking Receptors and Uses Thereof " filed on April 12, 1999 and assigned U.S.S.N. 09/290,376 (pending).

Please re-write the paragraph beginning on page 40, line 27, as follows:

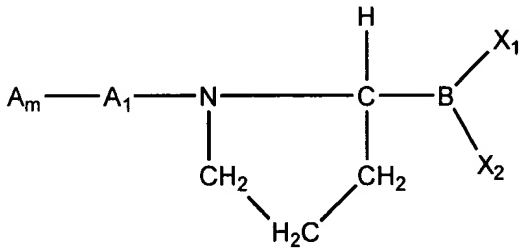
Identifying compounds and administration regimens which favor proliferation inhibition over hemopoietic stimulation, including dosing amounts, dosing schedules and routes of administration, involves comparison of results of the above assays to hemopoietic stimulation assays described previously in U.S. Patent Application Serial No. 09/304,199, filed May 3, 1999, entitled "Hematopoietic Stimulation", now issued as U.S. Patent No. 6,300,314, issued October 9, 2001, the contents of which are incorporated herein in their entirety by reference.

MARKED-UP CLAIMS

Please re-write the pending claims as follows:

1. (Amended) A method for treating a subject having a condition characterized by an abnormal mammalian cell proliferation, comprising:

administering to a subject in need of such treatment, a compound selected from the group consisting of an anti-angiogenic compound and an anti-cancer compound and an agent, in an amount effective to inhibit the proliferation, wherein the agent is a compound of [Formula I] Formula II



wherein m is an integer between 0 and 10, inclusive; A and A_1 are L- or D-amino acid residues; and each X_1 and X_2 is independently a hydroxyl group or a group capable of being hydrolyzed to a hydroxyl group in aqueous solution at physiological pH.

2. The method of claim 1, wherein the abnormal mammalian cell proliferation is manifested as a tumor.

3. The method of claim 1, wherein the condition is further characterized by the presence of reactive stromal fibroblasts.

4. The method of claim 1, wherein the abnormal mammalian cell proliferation is in epithelial cells.

5. The method of claim 4, wherein the abnormal mammalian cell proliferation is selected from the group consisting of a carcinoma, a sarcoma, and a melanoma.

6. The method of claim 1, wherein the condition is a metastasis of epithelial origin.

7. (Amended) The method of claim 1, wherein the condition is selected from the group consisting of breast cancer, colorectal cancer, ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma and fibrosarcoma.

8. The method of claim 1, wherein the condition is selected from the group consisting of bone and connective tissue sarcomas.

11. The method of claim 1, wherein the subject is otherwise free of symptoms calling for hemopoietic stimulation.

12. The method of claim 1, wherein the agent is administered in combination with surgery to remove an abnormal proliferative cell mass.

13. The method of claim 1, wherein the agent is administered to a patient who has had surgery to remove an abnormal proliferative cell mass.

14. The method of claim 1, wherein the agent is administered in combination with an anti-cancer compound.

15. The method of claim 1, wherein the agent is targeted to a tumor.

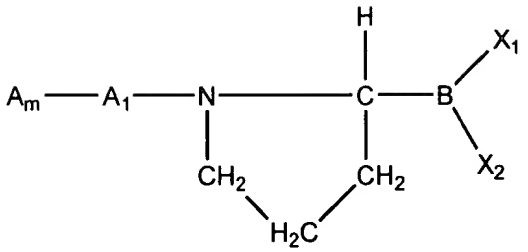
16. The method of claim 1, wherein the subject has normal hemopoietic activity.

17. The method of claim 1, wherein the subject is HIV negative.

18. The method of claim 1, wherein the agent is Val-boro-Pro.

19. (Amended) A method for inhibiting angiogenesis in a subject having a condition characterized by abnormal mammalian cell proliferation comprising:

administering to a subject in need of such treatment, a compound selected from the group consisting of an anti-angiogenic compound and an anti-cancer compound and an agent, in an amount effective to inhibit angiogenesis in an abnormal proliferative cell mass, wherein the agent is a compound of [of Formula I] Formula II

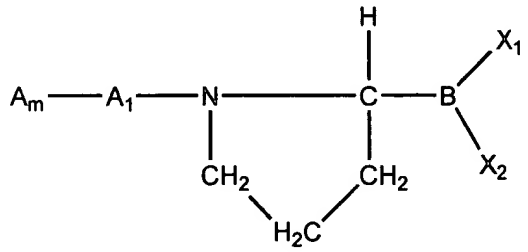


wherein m is an integer between 0 and 10, inclusive; A and A_1 are L- or D-amino acid residues; and each X_1 and X_2 is independently a hydroxyl group or a group capable of being hydrolyzed to a hydroxyl group in aqueous solution at physiological pH.

31. The method of claim 19, wherein the agent is administered in combination with an anti-angiogenic compound.

36. (Amended) A pharmaceutical preparation comprising:

an agent of [Formula I] Formula II



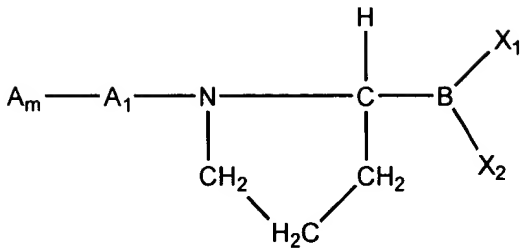
wherein m is an integer between 0 and 10, inclusive; A and A_1 are L- or D-amino acid residues; and each X_1 and X_2 is independently a hydroxyl group or a group capable of being hydrolyzed to a hydroxyl group in aqueous solution at physiological pH,

at least one other anti-cancer compound, and

a pharmaceutically acceptable carrier.

37. (Amended) A pharmaceutical preparation comprising:

an agent of [Formula I] Formula II



wherein m is an integer between 0 and 10, inclusive; A and A_1 are L- or D-amino acid residues; and each X_1 and X_2 is independently a hydroxyl group or a group capable of being hydrolyzed to a hydroxyl group in aqueous solution at physiological pH,

at least one other anti-angiogenic compound, and

a pharmaceutically acceptable carrier.